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RESEARCH ARTICLE

Preserved dynamic cerebral autoregulation in the middle cerebral artery among persons with migraine

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Abstract Migraine affects the autonomous nervous system and a recent investigation has also proposed a severe disturbance of dynamic cerebral blood flow regulation in the middle cerebral artery during spontaneous blood pressure oscillations. This study investigates whether dynamic cerebral autoregulation is impaired in persons with migraine among a normal cohort. Out of 94 adults studied to establish normal values for dynamic autoregulation, 19 suffered from migraine according to IHS criteria (10 of them with aura). Transcranial Doppler sonography and fingerplethysmography were used to determine dynamic autoregulation of both middle cerebral arteries following spontaneous low frequency (0.06–0.12 Hz) blood pressure fluctuations (phase and gain of transfer function, correlation coefficient indices Dx and Mx). No significant differences were found for the low frequency variability of blood pressure (power spectral density) and various indices of dynamic cerebral autoregulation between persons with and without migraine. Moreover, no differences were observed between persons with migraine, with and without aura. This study based on a normal cohort does not support the presence of generally impaired cerebral autoregulation dynamics in persons with migraine. Future studies should focus on posterior circulation and particular cerebellar autoregulation.

Keywords Migraine · Cerebral blood flow · Cerebral autoregulation

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Introduction

Silent ischemic brain lesions are more frequent in persons with migraine (Kruit et al. 2004). Many of these lesions occur in cerebellar vascular border zones suggesting other than pure embolic mechanisms (Kruit et al. 2005). In the middle cerebral artery territory, deep white matter lesions are also more frequent at least in women (Kruit et al. 2004). Amongst common findings like increased frequency of patent foramen ovale, the potential dysfunction of cerebral autoregulation as a cause for these ischemic lesions gained increasing interest. With disturbed autoregulation, episodes of low blood pressure may lead to transient cerebral hypoperfusion and impaired clearance of coinciding emboli in persons with migraine. Interestingly, the pathophysiology of migraine is linked to brainstem cerebral blood flow regulation structures (Weiller et al. 1995).

The assessment of cerebral autoregulation itself has experienced dramatic changes over the last decade. The introduction of transcranial Doppler sonography, which measures cerebral blood flow velocity (CBFV) noninvasively with a high-time resolution, lead to a concept assessing the dynamic regulatory response of

CBFV to transient changes in blood pressure (Aaslid et al. 1989; Panerai 1998). Such changes, however, already occur spontaneously in different frequency bands. In a low frequency range around 0.1 Hz, CBFV oscillations mirror the Mayer waves of blood pressure which reflect feedback oscillations of the baroreflex loop and sympathetic function. Methods in the frequency domain (transfer function analysis) (Zhang et al. 1998) and time domain (correlation coefficient method) (Czosnyka et al. 1996; Reinhard et al. 2003b) are used to differentiate cerebral autoregulation from these spontaneous fluctuations.

Using transfer function analysis, a recent study suggested a profoundly disturbed dynamic autoregulatory system in the middle cerebral artery in persons with migraine with values comparable to those of poorly compensated carotid artery occlusion (Müller and Marziniak 2005). Such a severe affection of the dynamic cerebral autoregulatory system would have important clinical implications and could contribute to the increased risk of cerebral ischemic lesions in migraine.

Within a cohort studied for establishing normal values of dynamic autoregulation, we identified persons with migraine and investigated whether the phenomenon of abolished autoregulation dynamics could be reproduced and confirmed with the time domain autoregulation method.

Methods

Ninety-four adults were recruited among the hospital staff and their relatives without prior focussing on any headache history. The measurement protocol was approved by the Local Ethics Committee beforehand, and all persons gave informed consent to participate in the study. A careful history regarding the presence of migraine was collected blinded to any autoregulation data from all persons by a standardized questionnaire. The presence of migraine with or without aura was determined according to the International Headache Society (IHS) criteria. Furthermore, a history on cardiovascular risk factors (hypertension, diabetes, hyperlipidemia) and medication was obtained from all persons. All subjects aged >40 years underwent carotid duplexsonography to exclude carotid artery stenosis affecting cerebral hemodynamics. All subjects suffering from migraine were free from a migraine attack on the day studied. Persons with migraine reported symptomatic treatment of attacks with nonsteroidal antiinflammatory drugs and triptans. None of them was on a migraine prophylactic medication.

Assessment of cerebral autoregulation

Measurements were performed in a supine position with 50° inclination of the upper body. Cerebral blood flow velocity (CBFV) was measured in both middle cerebral arteries by insonation through the temporal bone window with 2 MHz transducers attached to a headband (DWL-Multidop-X©, Germany). Continuous non-invasive arterial blood pressure (ABP) recording was achieved via a servo-controlled finger plethysmograph (Finapres© 2300, USA) with the subject's right hand positioned at the heart level. End-tidal CO_2 partial pressure was measured in mmHg with an infrared capnometer (Normocap©, Finland) during nasal expiration. After stable values had been established, a data segment of 10 min was recorded. Due to data artefacts, the mean length of eligible time series was 580 ± 67 s. Raw data were recorded at a sampling rate of 100 Hz. Further analysis was performed via custom-written software developed in-house.

Transfer function analysis (cross-spectral analysis)

We have previously described the methods in detail (Timmer et al. 1998). Power spectra SABP, SCBFV and the cross spectrum CS were estimated by transforming the time series of ABP and CBFV to the frequency domain via discrete Fourier transformation. Smoothing the respective periodograms resulted in the power spectra and CS estimates (for illustration see Fig. 1). With the smoothing used (triangular window of half-width eight frequency bins), the coherence

$$\mathrm{Coh}(f) = \frac{|\mathrm{CS}(f)|}{\sqrt{\mathrm{SABP}(f)\mathrm{SCBFV}(f)}}$$

(normalized modulus of CS) is significant at the 95% level if it exceeds 0.49.

The phase spectrum $\Phi(f)$ is the argument of the cross spectrum and is defined by

$$\mathrm{CS}(f) = |\mathrm{CS}(f)|\exp(i\Phi(f))$$

The gain can be interpreted as the regression coefficient of CBFV on ABP:

$$G(f) = \frac{|\mathrm{CS}(f)|}{\mathrm{SABP}(f)}$$

phase shift and gain were extracted from the low frequency range (0.06–0.12 Hz) automatically by averaging all frequency bins exhibiting a significant coherence. Furthermore, the mean power spectral

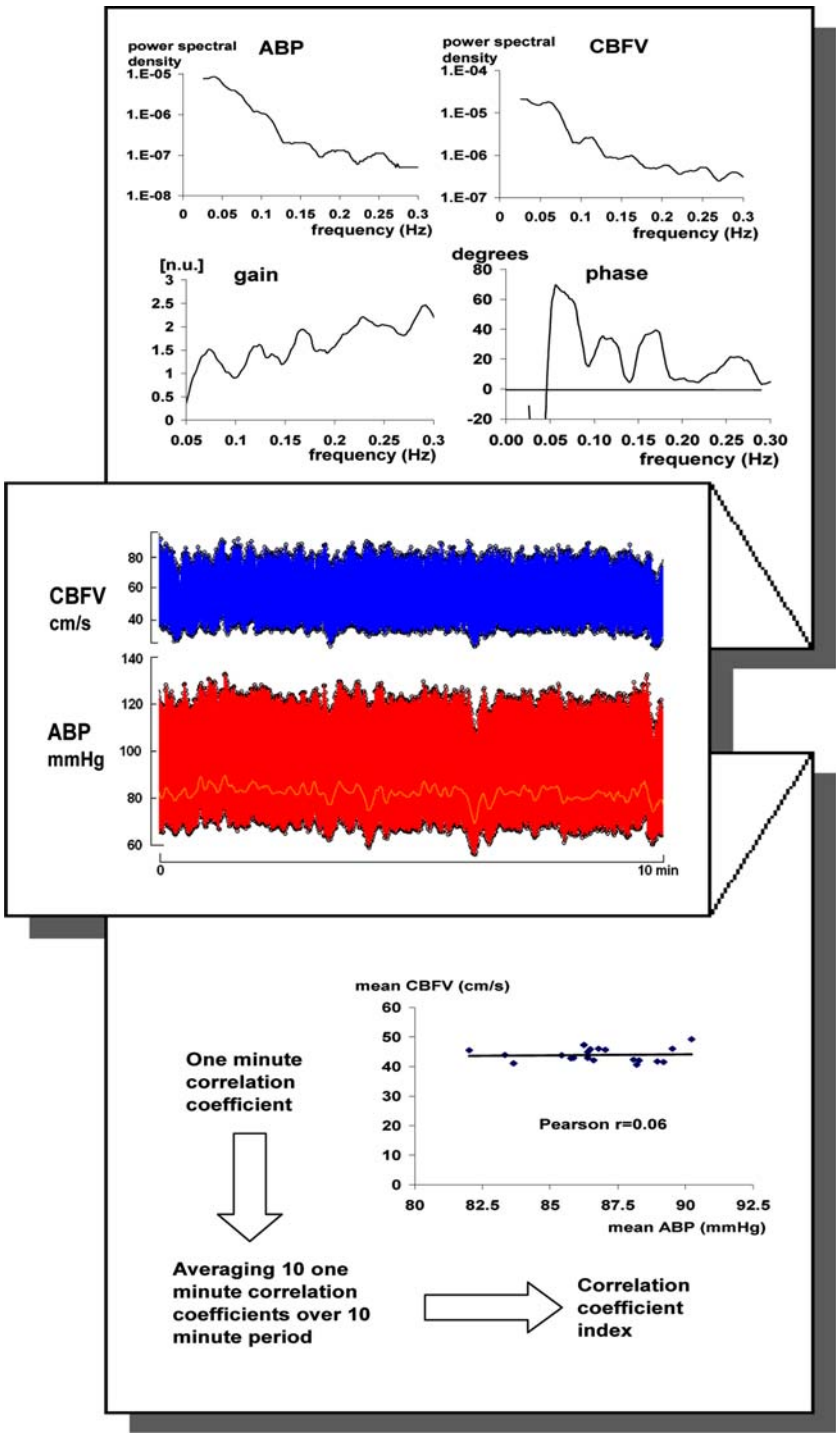

Fig. 1 Illustration of autoregulation analysis. Data of a 26-year-old man with migraine with aura. *Upper panel* shows power spectra of *ABP* and *CBFV* and transfer function analysis. A phase shift between slow oscillations of ABP and CBFV (with CBFV leading those of ABP) represents autoregulatory action by reflecting the continuous early counter-regulation of CBFV to its repetitive falls and rises during oscillating blood pressure (Kuo et al. 2003). Dynamic gain (normalized units) reflects the relative transmission of blood pressure oscillation amplitudes to the cerebral circulation, whereas a high gain indicates a reduced damping due to autoregulatory disturbance. *Lower panel* illustrates the concept of the correlation coefficient index method: a low correlation coefficient index indicates independency of CBFV from ABP and thus, intact autoregulation

density of ABP within the analyzed range was determined and normalized to the total length of the time series.

Correlation coefficient index analysis

This method of autoregulation testing makes use of the basic principle that increasing dependency of cerebral blood flow on blood pressure is mirrored by an increasingly positive correlation indicating vanishing autoregulatory activity (Czosnyka et al. 1996; Reinhard et al. 2003b). Thereby, diastolic and mean values of ABP and CBFV are first averaged over 3 s. Successively, 20 consecutive averaged values are used to calculate Pearson's correlation coefficient of diastolic and mean ABP and CBFV for 1 min periods of the

time series (see also Fig. 1). The sets of 1 min correlation coefficients are then averaged over the 10 min period yielding the autoregulatory indices Dx and Mx, respectively.

Statistical analysis

Intra- and inter-individual differences of autoregulatory measures were assessed using parametric tests after confirmation of normal distribution with the Kolmogorov–Smirnov test. Only power spectral densities failed to show normal distribution and were thus analyzed with the nonparametric Mann–Whitney test. Group differences were calculated with one-tailed Fisher's exact test. A general effect of migraine, hypertension and sex was assessed by multivariate analysis of variance (ANOVA). Equality of variances was confirmed using Levene's test. For the ANOVA, right and left autoregulatory values were averaged in persons with bihemispheric recordings. We report nominal P values without correction for multiple testing. A P value of less than 0.05 was considered statistically significant. Data are reported as mean ± SD.

Results

Nineteen persons (20%) fulfilled the IHS criteria of migraine. Baseline characteristics of the two groups are given in Table 1. Due to Doppler signal artefacts, bilateral recordings were not available in five controls and four migraineurs, one control had ABP signal artefacts impeding autoregulation analysis.

Figure 2 shows averaged phase and gain spectra of persons with and without migraine. Dynamic autoregulatory parameters are quantified in Table 2. No significant differences were observed for autoregulatory parameters between persons with and without migraine. Autoregulatory parameters also did not differ between migraine with or without aura. In persons with bilateral measurements, no significant side-to-side difference for any parameter occurred.

Hypertension and sex significantly differed between the migraine and control group. Multivariate analysis of variance using the factors migraine, hypertension and sex showed no significant influence of migraine and sex on any autoregulatory measure. Hypertension, however, was significantly associated with altered gain values ($P = 0.016$; average with hypertension: 0.67 ± 0.19 vs. 0.85 ± 0.30 without) but not with other autoregulatory values.

Discussion

Dynamic cerebral autoregulation can be analyzed from slow oscillations (Mayer waves) of arterial blood pressure. Slower oscillations of cerebral circulation below 0.05 Hz (so-called Brainstem-waves) may be accentuated in migraine patients indicating altered function of brain stem nuclei and sympathetic function (Sliwka et al. 2001). However, since these oscillations are usually not coherent with blood pressure oscillations they cannot be used for assessment of cerebral autoregulation (Kuo et al. 1998).

In the Mayer wave range, our migraine group had a phase shift and gain identical to non-migraineurs. This indicates intact dynamic autoregulation. Our results are confirmed by applying a second established method for autoregulation analysis from spontaneous blood pressure fluctuations (Czosnyka et al. 1996).

Reduced functional flow adaptation has been described in the middle cerebral artery territory in the interictal period of migraine with aura (Nedeltchev et al. 2004). Also, the vasoconstrictor reaction of the middle cerebral artery during exercise test is reduced in migraine with aura patients but not associated with altered cerebral blood flow velocities (Heckmann et al. 1998). Our present findings are, however, mainly in contrast to a recent study on cerebral autoregulation in 22 patients with migraine (Müller and Marziniak 2005).

Table 1 Baseline characteristics

	Migraine $n = 19$	Controls $n = 75$
Age (years)	54 ± 16	59 ± 13
Age range (years)	26–83	25–78
Sex male/female (n)	5/14	42/33*
Migraine with aura (n)	10	–
Migraine without aura (n)	9	–
Average number of attacks per month	1.5 ± 1.9	–
≥1 attack per month (n)	11	–
Mean ABP (mmHg)	76 ± 9	74 ± 14
Mean heart rate (beats/min)	66 ± 9	66 ± 9
Mean CBFV (cm/s) right	$n = 19$ 52 ± 8	$n = 74$ 49 ± 9
Left	$n = 16$ 54 ± 9	$n = 70$ 50 ± 9
Hypertension (n)	11	23*
Treated hypertension (n)	9	19*
Hyperlipidemia (n)	6	28
Statin treatment (n)	2	9
Diabetes (n)	2	6

The CBFV signal is derived from the middle cerebral artery and due to a missing transtemporal bone window not available on all sides in all persons. Blood pressure treatment consisted of beta blockers, diuretics, calcium antagonists, ACE inhibitors and sartanes as monotherapy or in various combinations

*$P < 0.05$ intergroup differences

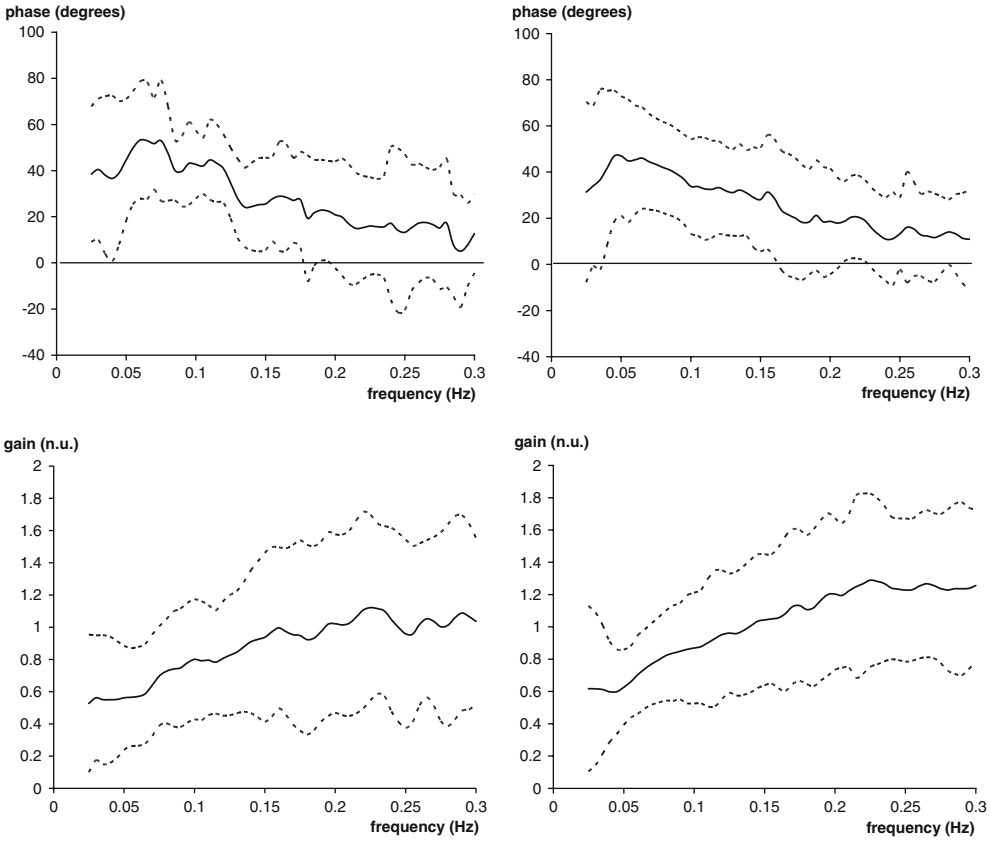

Fig. 2 Phase and gain spectra of persons with and without migraine. *Solid lines* denote mean values at each frequency bin, *dotted lines* ± one standard deviation. *Left column* pooled spectra of 19 migraineurs. *Right column* 74 persons without a history of migraine. In subjects with bilateral recordings, individual values were averaged. The relative gain (percentage change in CBFV by percentage change in ABP) is given in normalized units (n.u.)

Table 2 Autoregulatory parameters

The true *n* is varying due to artefacts and absence of coherency in individual persons impeding reliable extraction of phase and gain from the respective spectra. Eligible sides: transfer function analysis: migraine right $n = 16$, left $n = 17$, controls right $n = 71$, left $n = 69$; correlation coefficient analysis migraine right $n = 18$, left $n = 17$, controls right $n = 73$, left $n = 69$

		Migraine	Controls	Migraine versus controls
		$n = 19$	$n = 75$	*P* levels
Transfer function analysis (Low frequency range, 0.06–0.12 Hz)				
Phase (degrees)	Right	45.1 ± 12.8	39.1 ± 15.4	0.152
	Left	46.7 ± 12.6	40.5 ± 16.9	0.147
Gain (n.u.)	Right	0.74 ± 0.25	0.81 ± 0.27	0.356
	Left	0.72 ± 0.19	0.80 ± 0.28	0.250
ABP power spectral density (normalized units)		$2.76 \times 10^{-6} \pm 2.64 \times 10^{-6}$	$2.76 \times 10^{-6} \pm 2.67 \times 10^{-6}$	0.718
Correlation coefficient analysis				
Dx	Right	0.05 ± 0.13	0.06 ± 0.15	0.901
	Left	0.07 ± 0.12	0.06 ± 0.15	0.757
Mx	Right	0.26 ± 0.19	0.28 ± 0.18	0.679
	Left	0.32 ± 0.15	0.25 ± 0.16	0.134

In that study, persons with migraine showed an abnormally high power spectral density of ABP and CBFV oscillations even in the Mayer wave range (0.1 Hz: 1×10^{-3} in controls vs. 3×10^{26} in migraineurs) and a completely absent phase shift indicating abolished dynamic autoregulation. Principally, there are methodological differences, which may be highlighted by the huge differences of magnitudes between controls and migraineurs in ABP spectral measures in the previous study (factor 10^{29}). With our spectral analysis methodology (Reinhard et al. 2003a), we could not confirm such extremely altered power spectral densities in the Mayer wave range for ABP, which is in line with previous studies on patients with migraine (Pierangeli et al. 1997).

Apart from these methodological reasons, one basic reason for contrasting results might be the different selection of persons with migraines. In our study, aiming to establish normal values, migraineurs were not pre-selected but identified from a normal value

cohort. The prevalence of migraine and especially migraine with aura was comparatively high in this cohort. This might be an effect of chance but probably also be linked to a higher prevalence or awareness of migraine among neurologists (three of seven neurologists studied here) (Evans et al. 2003) and their relatives. Conversely, the migraine disease activity in our migraineurs might have been lower than that of preselected patients with migraine studied previously. A potential limitation of our study is that we did not focus on younger persons and the mean age is higher than in previous studies.

Because of the higher prevalence of migraine among women, the gender proportion between the two groups also differed significantly. One study found a higher transfer function gain in women (Wang et al. 2005). In the present study with a four times larger population, however, a significant effect of sex on any autoregulatory parameter was not confirmed. Hypertension was also more frequent in persons with migraine in the present sample. Controlling for hypertension in a multivariate analysis, migraine still did not show a significant influence on results. Hypertension, however, treated by various antihypertensive agents in most of the examined persons, showed an effect on transfer function gain with lower values. A previous study in persons with hypertension, off antihypertensive drugs, also showed a trend towards lower gain (=magnitude) values, which can be interpreted as a greater dampening of cerebral blood flow oscillations (Lipsitz et al. 2000). Future studies may clarify whether this could be an effect of hypertensive microvascular changes.

Even if autoregulation may be normal in the middle cerebral artery in the interictal period, it does not mean that autoregulation is normal in the posterior, particularly cerebellar circulation. Our results also do not exclude impaired middle cerebral artery autoregulation during the migraine attack.

The hypothesis of impaired cerebellar or posterior circulation autoregulation would pose a link to the increased rate of syncope and orthostatic intolerance despite normal orthostatic blood pressure and vascular border zone cerebellar lesions in migraineurs (Thijs et al. 2006; Kruit et al. 2005). A previous autoregulation study in the posterior cerebral artery in healthy adults showed that spontaneous blood pressure oscillations are less well dampened in that territory, while basilar artery regulation was normal using a step-wise blood pressure drop ('cuff deflation method') (Haubrich et al. 2004; Park et al. 2003). Cerebellar autoregulation, however, has not been investigated in migraineurs so far, and is even not extensively examined in healthy humans—probably because of difficulties in measuring cerebellar blood flow noninvasively. Yet, Dopplersonographic identification of the posterior inferior cerebellar artery (PICA) by a transnuchal approach seems feasible.

A basic susceptibility of the posterior circulation to hemodynamic impairment in migraine is already indicated by a disturbed interictal CO_2-reactivity in patients with migraine with aura (not in those without aura) in the basilar but not in the middle cerebral artery (Silvestrini et al. 2004). In general, CO_2-cerebrovascular reactivity has shown conflicting results in migraine. In the interictal period, a broad overlap with controls exists and CO_2-reactivity is probably higher than that of non-migraineurs both in the anterior and posterior circulation (Kastrup et al. 1998; Dora and Balkan 2002; Fiermonte et al. 1995), both in migraineurs with and without aura. During the attack, CO_2-reactivity seems to be vastly unchanged, even in the basilar artery in a patient group predominantly without aura (Zwetsloot et al. 1992). Virtually, CO_2 reactivity itself does not assess the intrinsic ability of the cerebral vasculature to regulate its flow in the face of changing blood pressures (i.e., cerebral autoregulation), but rather represents a quasi-pharmacological stimulation of cerebral arterioles and also certain brain stem nuclei, frequently leading to a concomitant blood pressure increase interacting with the pure arteriolar response (Dumville et al. 1998; Hetzel et al. 1999).

In conclusion, this study based on a normal cohort does not support the presence of generally impaired cerebral autoregulation dynamics in persons with migraine. In a next step, focussed investigation of posterior cerebral artery and particular cerebellar autoregulation in persons with migraine is needed. This may help in understanding the neurovascular pathophysiology of migraine and potentially contribute to characterizing migraine patients at special risk for posterior circulation ischemia.

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